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Flavor Aversions Induced by Chlordimeform

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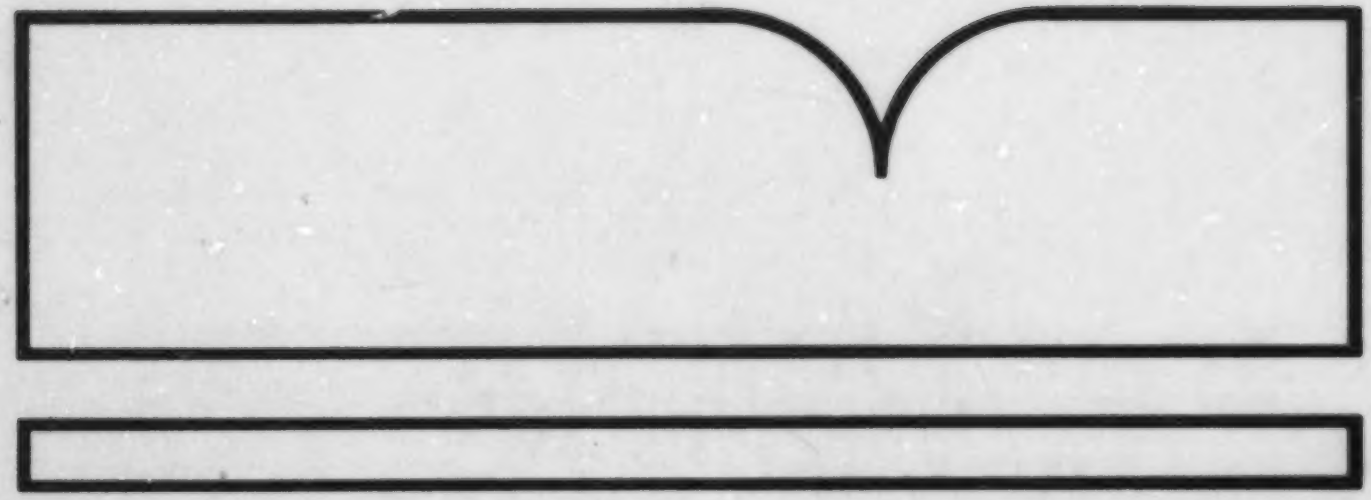

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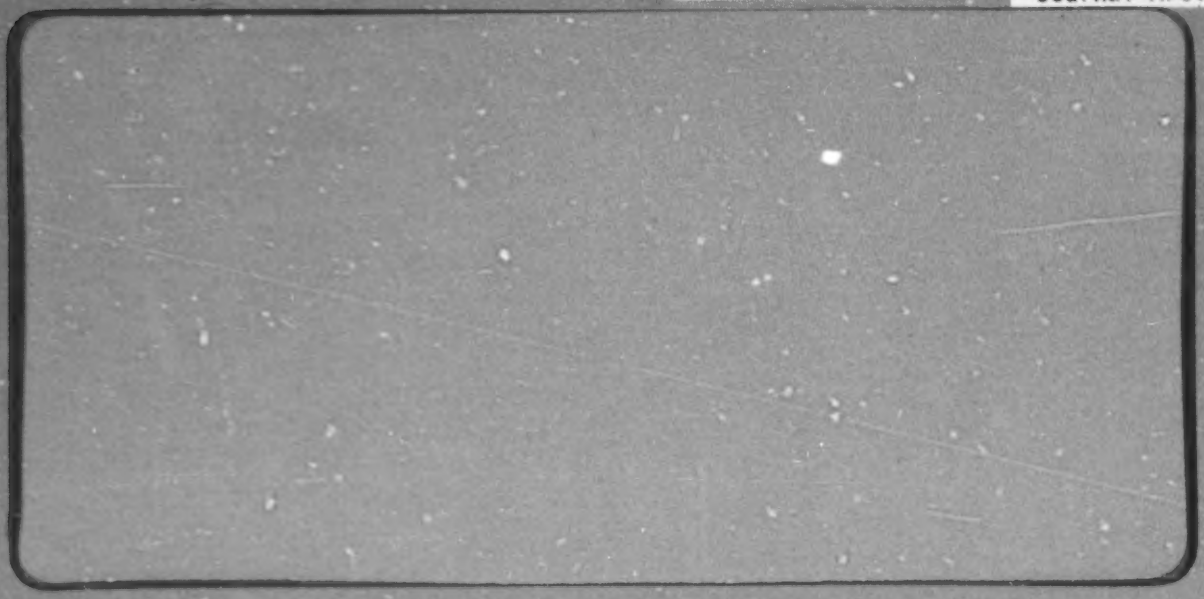

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16. ASSTRACT

CHLORDIMEFORM is a member of the formamidine class of insecticide/acaricide with many diverse pharmacological actions[2, 3, 7-11]. Little is known, however, about its behavioral actions, although evidence suggests that it produces signs of central nervous system stimulation[10,11]. The present study was undertaken, therefore, to further characterize the behavioral actions of chlordimeform. A flavor-aversion paradigm was selected because paradigms of this sort have already proven useful in assessing the behavioral impact of other types of toxic substances, e.g., methyl mercury[1,6,] lead and trienthyl-tin[5].

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Flavor Aversions Induced by Chlordimeform

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MACPHAIL, R. C. AND J. D. LEANDER. *Flavor aversions induced by chlordimeform.* NEUROBEHAV. TOXICOL. 2(4) 363–365, 1980.—Twenty-four rats were adapted to a daily one-half hour period of water availability. When intakes had stabilized, they were allowed access to water and to a 0.1% (w/v) solution of saccharin, and treated afterward in equal numbers with chlordimeform HCl (2.5, 5, or 10 mg/kg) or the saline vehicle. Three days later, all rats were again given access to both water and saccharin. Compared with saline control rats, those that had received chlordimeform displayed an aversion for saccharin that was proportional to the dosage. These data demonstrate the utility of a conditioned flavor aversion paradigm in assessing the behavioral effects of a formamidine insecticide.

Conditioned flavor aversion Chlordimeform Rats Flavor toxicosis

CHLORDIMEFORM is a member of the formamidine class of insecticide/acaricide with many diverse pharmacological actions [2, 3, 7–11]. Little is known, however, about its behavioral actions, although evidence suggests that it produces signs of central nervous system stimulation [10,11]. The present study was undertaken, therefore, to further characterize the behavioral actions of chlordimeform. A flavor-aversion paradigm was selected because paradigms of this sort have already proven useful in assessing the behavioral impact of other types of toxic substances, e.g., methyl mercury [1,6], lead and triethyl-tin [5].

METHOD

Animals

Twenty-four adult male Sprague-Dawley-derived rats, received from the Charles River Company (Charles River Breeding Laboratories, Portage, MI), were 75 days old at the start of the experiment. The rats were housed two to a cage (45×24×20 cm) in which food (Purina Laboratory Chow No. 5001, St. Louis, MO) was available ad lib throughout the experiment. Cages were located in a temperature-controlled (21±0.6°C) colony room in which lighting was provided from 0600 to 1800 hr daily.

Apparatus

Testing occurred in ceiling-suspended metal cages that measured 24.5×18×18 cm with a 1.3-cm wire mesh floor and front (Wahmann Mfg. Co., Timonium, MD). Fluids were provided in one or two 100-ml graduated glass bottles (Wahmann Mfg. Co) with rubber stoppers and straight metal drinking spouts. Each bottle was attached so that a rat could contact the spout *via* one of two small recesses (4×4×4 cm) attached to the front of the cage.

Procedure

The rats were acclimated to the animal colony room and after 6 days were placed on a 23-½ hour water-deprivation schedule. Under this schedule, each rat was weighed and transferred to a test cage in which tap water (21°C) was provided for 30 min; food was not available in the test cages. Water intake was calculated by subtracting the weight (to the nearest 0.1 g) of the water bottle (with sipper tube) after availability from that obtained prior to availability. The position of the water bottle was counterbalanced across animals for any one test day and across days for any one animal. All testing was carried out between 1300 and 1500 hr.

After 7 days of adaptation to the above conditions, all rats were provided with tap water and a 0.1% (w/v) sodium saccharin solution for one (exposure) session. Approximately 15 minutes after fluid availability had terminated, each rat was injected IP with chlordimeform HCl (kindly supplied by Nor-Am Agricultural Products, Woodstock, IL) or the isotonic saline vehicle. Chlordimeform was administered in dosages of 2.5, 5 and 10 mg of the salt/kg body wt. The volume of all injections was 1 ml/kg body wt. Six rats comprised each of the treatment groups; rats housed together received the same treatment.

Tap water was available as before for the next two daily sessions, whereas on the third (test) session all rats were again provided with a choice between water and the saccharin solution. Comparisons were made between vehicle- and chlordimeform-treated rats for total fluid intake (expressed in ml) and saccharin preference (expressed as a proportion of total intake). Statistical evaluations were carried out using a one-way analysis of variance.

RESULTS

Initial preferences for saccharin prior to the administra-

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tion of chlordimeform were weak and did not differ significantly between groups. Mean (±SEM) saccharin preferences for the groups that were to receive vehicle, 2.5, 5 and 10 mg/kg chlordimeform were 0.223 (±0.063), 0.405 (±0.127), 0.472 (±0.104), and 0.330 (±0.089), respectively. There were also no group differences in total fluid intake, which averaged about 20 ml.

Group differences in saccharin preference did emerge, however, following chlordimeform, as can be seen in Fig. 1. Compared with the vehicle-treated rats, those that received chlordimeform displayed an aversion to saccharin that was proportional to the dosage. For example, rats that received saccharin followed by saline subsequently displayed an average (±SEM) preference for saccharin of 0.824 (±0.053) whereas for those that received saccharin paired with 10 mg/kg chlordimeform, the corresponding value was 0.141 (±0.040). Figure 1 also shows that saccharin preference was not related to the total amount of fluid consumed during the test session.

DISCUSSION

Pairing saccharin availability with administration of chlordimeform produced subsequent aversions to saccharin whose magnitude was proportional to the dosage. These effects were obtained, moreover, in the absence of treatment-related differences in total fluid intake, indicating that the decreases in saccharin preference were not due to a non-specific toxic effect of chlordimeform. The possibility cannot be excluded, however, that social variables may have influenced the magnitude of the flavor aversion [4], since pair-housed rats received the same treatment. Nevertheless, these data indicate that the conditioned flavor-aversion paradigm can be used in assessing the behavioral effects of a formamidine insecticide, and as such are part of a growing literature on the applicability of flavor-aversion paradigms for evaluating a diverse array of chemicals [1, 5, 6].

Chlordimeform produced dose-related decreases in saccharin preference and these effects were obtained in the absence of overt somatic signs of intoxication. The median lethal dosage of chlordimeform was reported to be about 200 mg/kg when given intraperitoneally [9]. The effects obtained in the present experiment were produced by dosages that represent, therefore, a very small fraction of that required to produce lethality (less than 1/20th). These data suggest then that chlordimeform produces prominent behavioral effects at dosages that are well below those required for overt signs of intoxication.

The mechanism by which chlordimeform produces its behavioral effects is not known at this time. Chlordimeform has been shown to have diverse effects *in vitro* including inhibition of prostaglandin synthetase, inhibition of DNA, RNA and protein synthesis, respiratory uncoupling, and monoamine oxidase inhibition [8]. Equally diverse effects have been obtained *in vivo* including decreased blood pressure and cardiac contractility as well as antipyretic and anti-inflammatory effects [7,12]. In addition, changes in brain electrical activity and seizures produced by chlordimeform have been reported to be similar to those produced by local anesthetics [2,11]. Additional research, employing different behavioral paradigms, as well as pharmacological probes, is required to comprehensively assess the mechanism(s) responsible for the behavioral effects of chlordimeform.

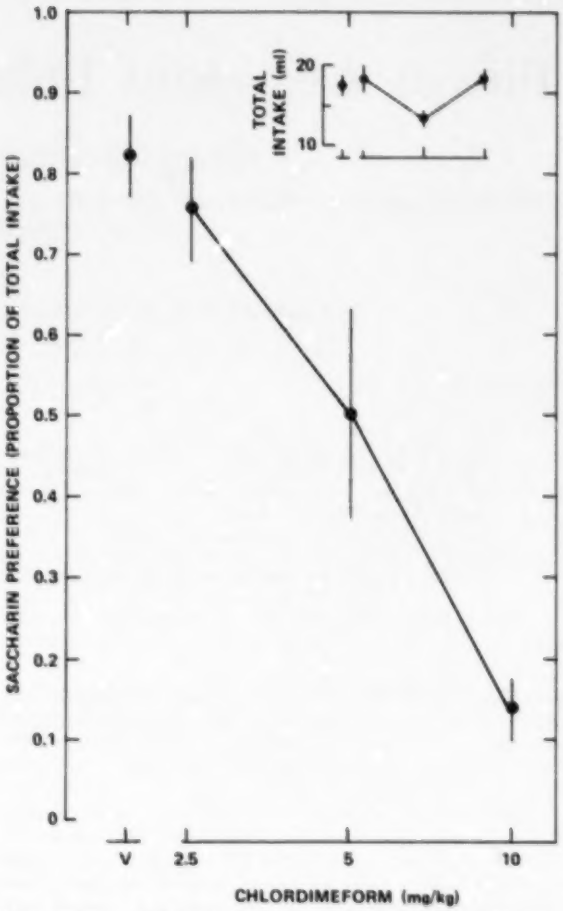

FIG. 1. Effects of chlordimeform on saccharin preferences in rats. Each symbol represents the average effect of chlordimeform (2.5–10.0 mg/kg) or the normal saline vehicle (V) on saccharin preference, expressed as a proportion of total intake, for groups of 6 rats. Vertical bars represent ±1 SEM. Insert presents corresponding data on total fluid intake for each treatment group during the test session. Chlordimeform produced a significant effect on saccharin preference, $F(3,20)=14.7$, $p<0.001$, but not on total intake ($p>0.20$).

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